Treatments that improve outcome in the patient with heart failure, left ventricular systolic dysfunction, or both after acute myocardial infarction

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Patients with heart failure, left ventricular systolic dysfunction, or both, after acute myocardial infarction have a poor prognosis. It is important to focus treatment on this high risk group to reduce the persistently high morbidity and mortality after acute myocardial infarction. As in chronic heart failure, there is now good evidence that inhibition of the renin–angiotensin–aldosterone system and sympathetic nervous system, with the appropriate drugs, can reduce morbidity and mortality. In addition to angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and β blockers, the aldosterone blocker eplerenone has now been shown to be effective in reducing adverse outcomes.

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Many studies show that patients with clinical evidence of heart failure or imaging evidence of substantial left ventricular systolic dysfunction (LVSD) early after acute myocardial infarction (AMI) have a poor subsequent prognosis.[1–6] In one of the most recent of these, an international registry collected in conjunction with a clinical trial, the adjusted hazard ratio for death during admission in patients with an AMI complicated by heart failure, LVSD, or both, was 4.12.[6] Remarkably, 80% of inpatient deaths occurred in this subset of high risk individuals who accounted for 42% of all patients with an AMI in the registry.[6] Morbidity, especially the subsequent development of chronic heart failure, is also particularly high in this patient subset.[1–6] These findings emphasise the importance of focusing treatment on patients with LVSD, heart failure, or both in order to reduce the persistently high morbidity and mortality after AMI.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Three landmark studies published in the early 1990s demonstrated the effectiveness of long term treatment with an angiotensin converting enzyme (ACE) inhibitor in reducing the risk of death, heart failure and, unexpectedly at the time, the risk of recurrent infarction in patients with LVSD, heart failure, or both after AMI (fig 1).[7–10] Other studies showed a smaller benefit with short term treatment in a much broader patient population after AMI.[11] However, these studies with broader inclusion criteria demonstrated a greater absolute benefit in higher risk patients. Importantly, they showed that treatment could be started, safely, early after the onset of infarction and that a reduction in death was seen within the first few days of treatment.[11] The findings of these trials are reflected in all major guidelines which advocate early initiation and long term treatment with an ACE inhibitor in patients with LVSD, heart failure, or both after AMI.[12 13] This recommendation is given the highest level of evidence. The absolute morbidity and mortality benefit of such treatment is substantial (table 1).

β BLOCKERS

Despite being the first evidence based treatment for AMI, on the basis of key trials conducted in the 1970s and 1980s, physicians had been reluctant to give β blockers to patients with LVSD, heart failure, or both.[10 14 15] In retrospect, it seems that such patients were probably passively excluded by investigators from the early β blocker trials and there was undoubtedly some clinical concern that β blocker treatment might worsen ventricular function or heart failure in these patients. Consequently, for example, only 25% of patients in SAVE, AIRE, and TRACE were treated with a β blocker.[10] As a result of the parallel discovery that β blockers could not only be used safely in patients with *chronic* heart failure but also substantially reduced morbidity and mortality in those patients, a new β blocker trial in AMI was conducted. In that study, CAPRICORN, patients with LVSD (and with or without heart failure) were randomised to placebo or carvedilol.[16] All patients were treated, according to guidelines, with an ACE inhibitor. In other words, CAPRICORN tested whether a β blocker would give added benefit on top of the best, evidence based, background treatment. Compared with placebo, there was a 23% relative risk reduction

Abbreviations: ACE, angiotensin converting enzyme; AIRE, acute infarction ramipril efficacy; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAPRICORN, carvedilol post infarct survival control in left ventricular dysfunction; CARE, cholesterol and recurrent events; EPHESUS, eplerenone neurohormonal efficacy and survival study; 4S, Scandinavian simvastatin survival study; LIPID, long-term intervention with pravastatin in ischemic disease; LVSD, left ventricular systolic dysfunction; OPTIMAAL, optimal trial in myocardial infarction with the angiotensin II antagonist losartan; SAVE, survival and ventricular enlargement; TRACE, trandolapril cardiac evaluation study; VALIANT, valsartan in acute myocardial infarction trial

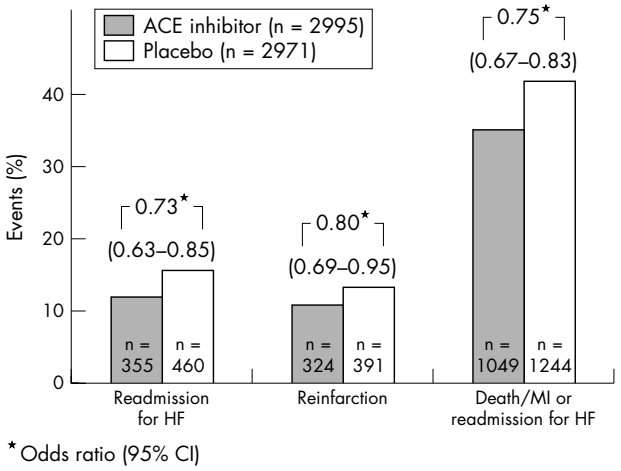

Figure 1 Effect of angiotensin converting enzyme (ACE) inhibitors on fatal and non-fatal cardiovascular events in survivors of acute myocardial infarction with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction. Adapted from Flather *et al*.[10]

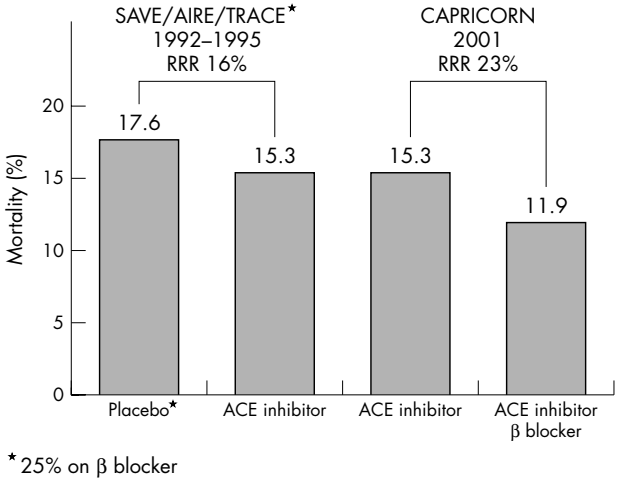

Figure 2 Incremental benefit of adding a β blocker to an ACE inhibitor in survivors of acute myocardial infarction with left ventricular systolic dysfunction, heart failure, or both. One year event rates are shown for SAVE/AIRE/TRACE.

in mortality with carvedilol and a reduction in re-infarction (but not, curiously, in heart failure).

This finding, taken in conjunction with the ''pre-ACE inhibitor era'' β blocker trials and the new chronic heart failure β blocker trials, argues persuasively for routine, combined, ACE inhibitor and β blocker treatment for patients with LVSD, heart failure, or both after AMI (fig 2). This evidence is also reflected in guideline recommendations.[12 13]

ANGIOTENSIN RECEPTOR BLOCKERS

Because it was thought that angiotensin receptor blockers (ARBs) might be more effective than ACE inhibitors in reducing the harmful effects of angiotensin II, two trials, OPTIMAAL and VALIANT, were designed to compare these two types of treatment.[17 18] Also, because there were theoretical reasons to believe that both drugs together might be better than either alone, one of these trials, VALIANT, also compared combination ACE inhibitor and ARB treatment to each monotherapy.[18] Neither trial showed that the ARB tested was superior to the ACE inhibitor tested (captopril).[17 18] VALIANT did, however, show that valsartan was as effective as captopril, providing an alternative for patients unable to tolerate an ACE inhibitor—for example, because of cough (fig 3).[18] Combination valsartan and captopril was not better than captopril alone.

ALDOSTERONE BLOCKADE

The other effector hormone in the renin–angiotensin system is aldosterone; aldosterone blockade is known to reduce substantially mortality in severe *chronic* heart failure.[19] Consequently, this therapeutic approach was also tested in AMI.[20] In the EPHESUS trial, patients with LVSD *and* heart failure (or diabetes mellitus) were randomised to receive placebo or eplerenone added to full conventional background treatment (including an ACE inhibitor/ARB in 86% of cases and β blocker in 75% of cases).[20] Eplerenone treatment led to a 15% relative risk reduction in all cause mortality as well as to a reduction in hospital admission for cardiovascular reasons, especially heart failure (fig 4, table 1). The benefit of eplerenone was seen across all subgroups of patients, including those treated with all of an ACE inhibitor (or ARB), a β blocker, aspirin, a statin, and coronary reperfusion therapy—that is, the benefit was clearly obtained over and above that of the best available background treatment (fig 4).

OTHER PHARMACOLOGICAL TREATMENTS

Though the high risk subset of patients discussed in this overview have, to some extent, been excluded from prior statin trials, there is no good reason to believe that this treatment should be ineffective in patients with LVSD, heart failure, or both. The ongoing CORONA trial in *chronic* heart

Table 1 Absolute benefit of evidence based pharmacological treatments of patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction

Trials	Treatment	Duration of follow up (years)	Events avoided per 1000 patients treated*		
			Deaths	Acute MI	Heart failure
SAVE, AIRE, TRACE meta-analysis	ACE inhibitor	2.6	57	23	36
CAPRICORN	β Blocker	1.3	34	23	–
EPHESUS	Aldosterone blocker	1.3	23	–	14

*Events avoided relates to the *number* of patients avoiding event; more *episodes* than this were avoided—for example, there were 43 fewer hospital admissions for heart failure per 1000 patients treated with eplerenone (as opposed to 14 fewer patients hospitalised for heart failure). Note: (1) Different duration of follow up; deaths avoided per 1000 *patient years* would be: 22 with an ACE inhibitor, 26 with a β blocker, 18 with an aldosterone blocker. (2) Events are not mutually exclusive; for the composite of death or acute MI, 66 fewer patients per 1000 treated experienced this composite with an ACE inhibitor and 53 fewer with a β blocker; for death, MI, or heart failure the number was 69 with an ACE inhibitor.

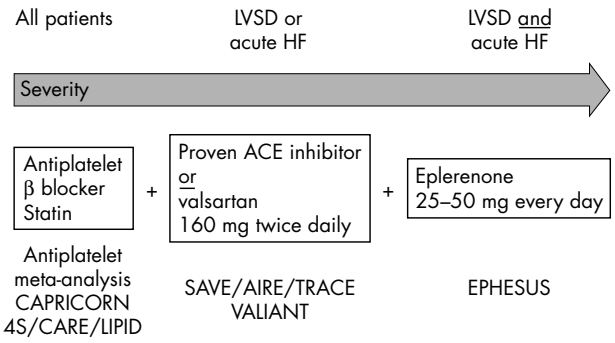

Figure 3 An evidence based algorithm for the early treatment of acute myocardial infarction complicated by left ventricular systolic dysfunction, heart failure, or both.

failure will, however, provide more evidence which may help answer this question.[21] Similarly, antiplatelet treatment has not been specifically studied in patients with LVSD, heart failure, or both. Furthermore, there has been considerable debate about whether aspirin might attenuate the benefits of ACE inhibitors and this argument remains unresolved.[22 23] Agents which do not inhibit cyclo-oxygenase—for example, clopidogrel—should not have this theoretical disadvantage of aspirin.

CONCLUSION

Patients with LVSD, heart failure, and especially both remain at remarkably high risk and account for the majority of both short and long term fatal and non-fatal outcomes in patients with AMI. Effective treatments—capable of substantially reducing these adverse outcomes—exist, the latest of which is eplerenone (fig 3). The challenge to physicians is to ensure that this wealth of evidence is applied in practice so that the individual patient and society benefits.

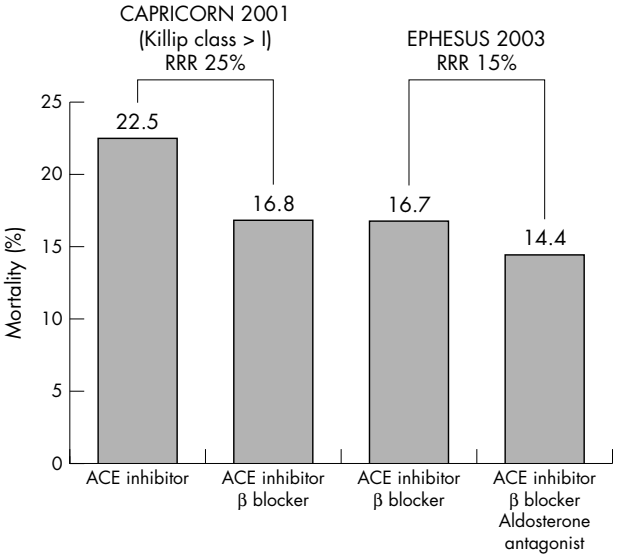

Figure 4 Incremental benefit of adding an aldosterone blocker to an ACE inhibitor in survivors of acute myocardial infarction with left ventricular systolic dysfunction *and* acute heart failure. EPHESUS is compared to the subset of CAPRICORN patients in Killip class I or greater at baseline.

Learning points

- Patients with heart failure, left ventricular systolic dysfunction, or both, after acute myocardial infarction (AMI) have a poor prognosis and it is important to focus treatment on this high risk group to reduce the persistently high morbidity and mortality after AMI
- As in chronic heart failure, there is now good evidence that pharmacological inhibition of the renin–angiotensin–aldosterone system and sympathetic nervous system can reduce morbidity and mortality
- In addition to angiotensin converting enzyme inhibitors, angiotensin receptor blockers and β blockers, the selective aldosterone blocker eplerenone has now been shown to be effective in reducing adverse outcomes
- The wealth of evidence from clinical trials now needs to be applied in practice

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REFERENCES

1 **Gottlieb S**, Moss AJ, McDermott M, *et al*. Interrelation of left ventricular ejection fraction, pulmonary congestion and outcome in acute myocardial infarction. *Am J Cardiol* 1992;**69**:977–84.
2 **Spencer FA**, Meyer TE, Goldberg RJ, *et al*. Twenty year trends (1975–1995) in the incidence, in-hospital and long-term death rates associated with heart failure complicating acute myocardial infarction: a community-wide perspective. *J Am Coll Cardiol* 1999;**34**:1378–87.
3 **Spencer FA**, Meyer TE, Gore JM, *et al*. Heterogeneity in the management and outcomes of patients with acute myocardial infarction complicated by heart failure: the National Registry of Myocardial Infarction. *Circulation* 2002;**105**:2605–10.
4 **Wu AH**, Parsons L, Every NR, Bates ER, Second National Registry of Myocardial Infarction. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the second national registry of myocardial infarction (NRMI-2). *J Am Coll Cardiol* 2002;**40**:1389–94.
5 **Kashani A**, Giugliano RP, Antman EM, *et al*. Severity of heart failure, treatments, and outcomes after fibrinolysis in patients with ST-elevation myocardial infarction. *Eur Heart J* 2004;**25**:1702–10.
6 **Velazquez EJ**, Francis GS, Armstrong PW, VALIANT Registry, *et al*. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry. *Eur Heart J* 2004;**25**:1911–9.
7 **Pfeffer MA**, Braunwald E, Moye LA, *et al*. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE investigators. *N Engl J Med* 1992;**327**:669–77.
8 **The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators**. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**:821–8.
9 **Kober L**, Torp-Pedersen C, Carlsen JE, *et al*. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril cardiac evaluation (TRACE) study group. *N Engl J Med* 1995;**333**:1670–6.
10 **Flather MD**, Yusuf S, Kober L, *et al*. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-inhibitor myocardial infarction collaborative group. *Lancet* 2000;**355**:1575–81.
11 **ACE Inhibitor Myocardial Infarction Collaborative Group**. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation* 1998;**97**:2202–12.
12 **Van de Werf F**, Ardissino D, Betriu A, *et al*. Task force on the management of acute myocardial infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The task force on the management of acute myocardial infarction of the European Society of Cardiology. *Eur Heart J* 2003;**24**:28–66.
13 **Antman EM**, Anbe DT, Armstrong PW, *et al*, American College of Cardiology; American Heart Association; Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004;**44**:671–719.

14 **Houghton T**, Freemantle N, Cleland JG. Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction? A meta-regression analysis of randomised trials. *Eur J Heart Fail* 2000;**2**:333–40.
15 **Lichstein E**, Hager WD, Gregory JJ, *et al*. Relation between beta-adrenergic blocker use, various correlates of left ventricular function and the chance of developing congestive heart failure. The multicenter diltiazem post-infarction research group. *J Am Coll Cardiol* 1990;**16**:1327–32.
16 **Dargie HJ**. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90.
17 **Dickstein K**, Kjekshus J, OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal trial in myocardial infarction with angiotensin II antagonist losartan. *Lancet* 2002;**360**:752–60.
18 **Pfeffer MA**, McMurray JJ, Velazquez EJ, *et al* Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–906.
19 **Pitt B**, Zannad F, Remme WJ, *et al*. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. *N Engl J Med* 1999;**341**:709–17.
20 **Pitt B**, Remme W, Zannad F, *et al* Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–21.
21 **Dunselman P**, Hjalmarson A, Kjekshus J, *et al*. Executive Committee of the CORONA trial. The statin wars. *Lancet* 2003;**362**:1854.
22 **Latini R**, Tognoni G, Maggioni AP, *et al*. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomized patients. Angiotensin-converting enzyme inhibitor myocardial infarction collaborative group. *J Am Coll Cardiol* 2000;**35**:1801–7.
23 **Teo KK**, Yusuf S, Pfeffer M, *et al* ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002;**360**:1037–43.